PETITIONS-520





BOX PATENT EXT.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH, *et al.*

Assignee: Sepracor, Inc.

Issue Date: November 8, 1994



REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Sepracor, Inc. ("Sepracor"), represents that it is the owner of record of United States Patent No. 5,362,755 and hereby requests an extension of the patent term of U.S. Patent No. 5,362,755.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. §1.740, and follows the format and requirements set forth in 37 C.F.R. § 1.740.

06/01/1999 LBOND1 00000004 5362755
01 FC:111 1120.00 OP

**(1) "A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics." 37 C.F.R. §1.74(a)(1)**

The approved product is XOPENEX™ (Levalbuterol hydrochloride), inhalation solution. The generic name for the approved product is levalbuterol hydrochloride, which is indicated for the treatment or prevention of bronchospasm in adults and adolescents with reversible obstructive airway disease. Synonyms for Levalbuterol hydrochloride are:

(-)-Albuterol hydrochloride;

(R)-Albuterol hydrochloride;

Levosalbutamol hydrochloride

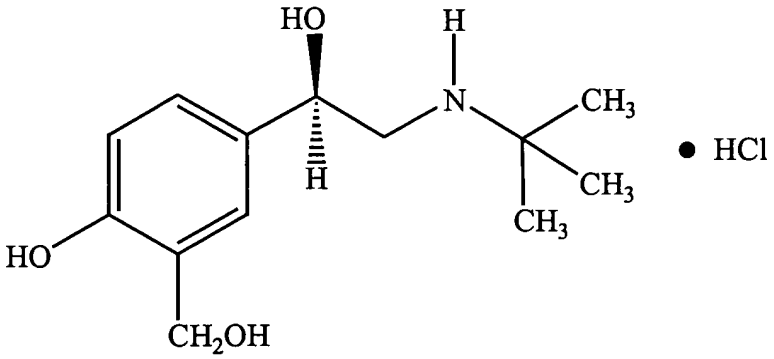
(R)- Salbutamol hydrochloride.

(-)-Salbutamol hydrochloride and

(R)-(-)-Salbutamol hydrochloride.

The Levalbuterol HC1 is identified by the following:

(a) Structural Formula:



(b) Chemical Names:

(R)-$\alpha^1$-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride;

$\alpha^1$-((tert-butylamino)methyl)-4-hydroxy-m-xylene-$\alpha$,$\alpha^1$-diol hydrochloride; and

($\alpha^1$R)-$\alpha^1$-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride.

(c) Molecular Weight: 275.8

(d) Empirical Formula: $C_{13}H_{21}NO_3 \bullet HCl$

**(2) "A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred, " 37 C.F.R. § 1.740(a)(2).**

Section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 355, is the Federal statute under which the Food and Drug Administration's (FDA's) regulatory review of Sepracor, Inc.'s XOPENEX™ new drug application (NDA) for Levalbuterol hydrochloride occurred. Section 505(b) of the FDC Act, 21 U.S.C. § 355(b), authorizes the filing of an NDA for a "new drug." FDA subsequently approved the XOPENEX™ NDA (NDA 20,837) under the authority granted the agency by Section 505(c) of the FDC Act, 21 U.S.C. & 355 (c).

**(3) "An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred," 37 C.F.R. § 1.740(a)(3).**

On March 25, 1999, the FDA approved Sepracor's XOPENEX™ (Levalbuterol hydrochloride) NDA under section 505 of the FDC Act. Approval of the NDA authorizes the first commercial marketing of Levalbuterol hydrochloride.

**(4) "In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved," 37 C.F.R. § 1.740(a)(4).**

The active ingredient in Levalbuterol hydrochloride Inhalation Solution is levalbuterol. Levalbuterol has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act the Public Health Service Act or the Virus-Serum-Toxin Act. Levalbuterol is the levorotatory enantiomer of the racemic mixture albuterol. Albuterol has been previously approved by the FDA.

The U.S. Patent and Trademark Office and the Food and Drug Administration have taken the position that an enantiomer has not been "previously approved" for commercial marketing or use by the FDA although the racemate has been previously approved by the FDA. This is shown in the attached letters of communication between the U.S. Patent and Trademark Office (USPTO) and the Food and Drug Administration that determined that the approval of dexfenfluramine hydrochloride was considered to be the first permitted commercial marketing or use of the approved product, although the racemate fenfluramine had been previously approved. (Exhibit F). The July 10, 1996, letter from Hiram Bernstein of the USPTO Office of the Deputy Assistant Comissioner for Patent Policy and Projects to Ronald L. Wilson at the FDA and a response from Mr. Wilson dated November 21, 1996, to Stephen G. Kunin in that same office of the USPTO, show that the approval of the dexfenfluramine hydrochloride enantiomer was determined to be the first permitted commercial marketing or use of the enantiomer product.

**(5) "A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted," 37 C.F.R. § 1.740(a)(5)**

This application is being submitted within the sixty day period following FDA approval of the XOPENEX™ (Levalbuterol hydrochloride) NDA. FDA approved the XOPENEX™ (Levalbuterol hydrochloride) on March 25, 1999. The sixty day period for submission of this patent extension application will expire on May 24, 1999.

**(6) "A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration," 37 C.F.R. § 1.740(a)(6).**

| | |
|---|---|
| U.S. Patent No. | 5,362,755 |
| Inventor: | Timothy J. Barberich |
| Issue Date: | November 8, 1994 |
| Expiration Date: | November 8, 2011 |

**(7) "A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings," 37 C.F.R. § 1.740(a)(7).**

A copy of U.S. Patent 5,362,755 is attached as Exhibit A.

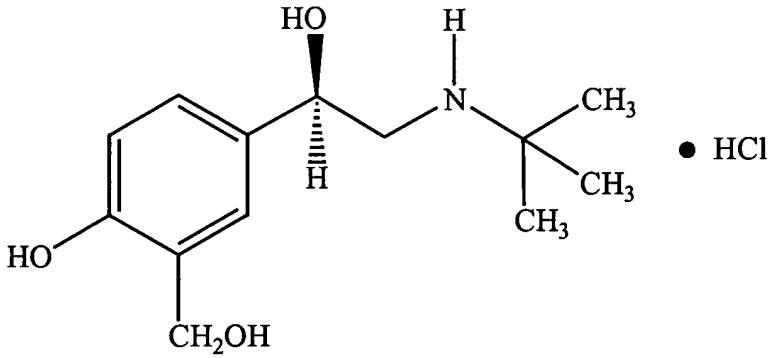
**(8) "A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent," 37 C.F.R. § 1.740(a)(8).**

U.S. Patent 5,362,755 issued on November 8, 1994 and the first maintenance fee was paid May 6, 1998. A copy of the printout of the Maintenance Status showing the payment is attached as Exhibit B.

No disclaimer, certificate of correction or re-examination certificate has issued in connection with U.S. Patent No. 5,362,755.

**(9) "A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product," 37 C.F.R. § 1.740(a)(9).**

U.S. Patent No. 5,362,755 claims a method of using the approved product levalbuterol hydrochloride. U.S. Patent No. 5,362,755 claims the approved indication for using levalbuterol hydrochloride. Claims 1, 2, 3, 6 and 7 are directed to the approved method of using levalbuterol hydrochloride for treating an individual with asthma. Levalbuterol hydrochloride is a pharmaceutically acceptable salt of (R)-$\alpha^1$-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride and has the following formula:




Representative claims from U.S. Patent 5,362,755 are reproduced below.

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(-) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(-) isomer of albuterol is greater than 99% by weight of total albuterol.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

The labeling approved by the FDA for Levalbuterol hydrochloride Inhalation Solution, which is marketed under the trade name Xopenex™, states that the drug is "indicated for the treatment or prevention of bronchospasm in adults and adolescents 12 years of age and older with reversible obstructive airway disease." The Clinical Pharmacology section of the FDA approved labeling includes a statement that "Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges."

The Drug Interaction section of the FDA approved labeling includes a statement that "[o]ther short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol." The labeling listed the following drugs to be used with

caution if added to levalbuterol HCl: (1) adrenergic drugs; (2) beta-adrenergic receptor blocking agents; (3) non-potassium sparing diuretics and (4) digoxin. Both claims 6 and 7 cover a condition of use that is included within the approved indication for Xopenex™ when (a) at least one additional drug selected from the group of bronchodilators, antihistamines and analgesics is added to the levalbuterol or (b) an adrenergic drug, a beta-adrenergic receptor blocking agent; a non-potassium sparing diuretic or digoxin is added to levalbuterol HCl with caution.

**(10) "A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services . . . to determine the applicable regulatory review period . . . For a patent claiming a human drug . . . the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) . . . was initially submitted and the NDA . . . number and the date on which the NDA was approved" 37 C.F.R. § 1.740(a)(10)(i).**

In order to enable the Secretary to determine the applicable regulatory review period, the following information is provided.

(a) Sepracor, Inc. filed its Investigational New Drug (IND) application on February 28, 1995, for XOPENEX™ (Levalbuterol hydrochloride) and it became effective on March 30, 1995.

(b) Sepracor, Inc. initially submitted a new drug application (NDA) for XOPENEX™ (Levalbuterol hydrochloride) to the FDA on June 30, 1997, where it was received on July 1, 1997.

(c) XOPENEX™ (Levalbuterol hydrochloride) was approved by the FDA on March 25, 1999.

**(11) "A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities" 37 C.F.R. § 1.740(a)(11).**

Attached is a chronology that briefly describes the significant regulatory activities and relevant dates associated with Sepracor, Inc.'s efforts to seek approval of this product before the FDA (Exhibit C).

**(12) "A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined," 37 C.F.R. § 1.740(a)(12).**

Statement of Eligibility of the Patent for Extension

(i) It is the opinion of the applicant that U.S. Patent 5,362,755 is eligible for an extension. This opinion is based on the following information on U.S. Patent No. 5,362,755:

(a) 35 U.S.C. § 156(a) - U.S. Patent No. 5,362,755 claims the approved human drug product XOPENEX™ (Levalbuterol hydrochloride).

(b) 35 U.S.C. § 156 (a)(1) - The term of the patent has not expired prior to the submission of this application.

(c) 35 U.S.C. § 156 (a)(2) - The term of said patent has never been previously extended under 35 U.S.C. § 156 (e)(1).

(d) This application for extension is in compliance with 37 C.F.R. § 1.740.

(e) 35 U.S.C. § 156(a)(4) - The product, XOPENEX™ (Levalbuterol hydrochloride), has been subject to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The product received permission for commercial marketing or use under the provision of law (i.e., FDC Act § 505) under which the applicable regulatory review occurred.

(g) The application has been submitted within sixty days from the March 25, 1999, approval date.

(h) 35 U.S.C. § 156(c)(4) - No other patent term has been extended for the same regulatory review period for this product.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 5,362,755 should be extended by 1 year, 137 days, or until March 25, 2013. This term of extension was determined on the following bases.

First, the following calculation of the regulatory review period is in accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.775. The length of this extension was determined as follows:

(A) The effective date of the Investigational New Drug (IND) application is March 30, 1995, which was thirty days after FDA receipt of the IND on February 28, 1995. The IND number is 47,303.

(B) The new drug application (NDA) for XOPENEX™ (NDA 20-837) was initially submitted to the FDA on June 30, 1997 and received by the FDA on July 1, 1997.

(C) The NDA was approved by the FDA on March 25, 1999.

(D) U.S. Patent No. 5,362,755 was issued on November 8, 1994, and is entitled to a patent term of 17 years from its issue date.

As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

> (i) the length of time between the date an exemption under §505(i) of the FFDCA became effective (the effective date of the IND) and the date an application was initially submitted under §505 of the FFDCA (the date of the initial submission of the NDA).

An IND for the product was effective on March 30, 1995. The NDA for the product was submitted on July 1, 1997. Thus, for the purpose of this calculation, item (i) for the product equals the number of days from March 30, 1995, to July 1, 1997, or 824 days.

(ii) the length of time between the date an application was initially submitted under §505(b) of the FFDCA (the date of the initial submission of the NDA) and the date the application was approved (the approval date of the NDA).

The NDA for the product was submitted on July 1, 1997. The NDA was approved on March 25, 1999. Thus, for the purpose of this calculation, item (ii) equals the number of days from July 1, 1997, to March 25, 1999, or 633 days.

In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which occurred after the date the patent issued. U.S. Patent No. 5,362,755 issued on November 8, 1994. The entire regulatory review period calculated above occurred after this date.

Second, 35 U.S.C. § 156(c) also sets forth the following exceptions (1) - (3) which may operate to shorten the length of the review period used to calculate patent term extension.

(1) Each period is reduced by any period during which the applicant did not act with due diligence.

There has been no lack of due diligence during the period of regulatory review. Accordingly, no reduction in the review period is required by this provision.

(2) Each period includes only one-half of the number of days in phase (i).

One-half of the number of days in phase (i) equals one-half of 824 days, or 412 days. Adding this number of days to the number of days in phase (ii) (633 days) results in a review period of 1045 days.

> (3) If the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

On the date of approval of the product, March 25, 1999, 12 years and 228 days remained in the term of U.S. Patent No. 5,362,755. Adding this period to the review period calculated above yields a period of more than fourteen years. This provision, therefore, shortens the period of extension to which U.S. Patent No. 5,362,755 is entitled, to fourteen years from March 25, 1999, or to March 25, 2013, which represents an extension of 1 year and 137 days.

Third, 35 U.S.C. § 156(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent No. 5,362,755 is November 8, 2011. Accordingly, the maximum extension allowed by this provision would extend the term to November 8, 2016. Extension of the patent by the number of days calculated above would not extend the patent beyond November 8, 2016. Accordingly, this provision does not operate to shorten the period of extension to which U.S. Patent No. 5,362,755 is entitled.

Thus, U.S. Patent No. 5,362,755 is entitled to an extension of 1 year and 137 days, to March 25, 2013.

**(13) "A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought," 37 C.F.R. § 1.740(a)(13).**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

**(14) "The prescribed fee for receiving and acting upon the application for extension," 37 C.F.R. § 1.740(a)(14).**

Pursuant to 37 C.F.R. § 1.20(j)(1), a check in the amount of $1,120.00 is enclosed with this application.

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees. Should a refund of fee paid be necessary, the Commissioner is hereby authorized to credit any such amount to Deposit Account No. 19-0741.

**(15) "The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed," 37 C.F.R. § 1.740(a)(15).**

Please direct all inquires and correspondence relating to this application for patent term extension to:

Harold C. Wegner
FOLEY & LARDNER
Washington Harbour, Suite 500
3000 K Street, N. W.
Washington, D. C. 20007-5109
TEL: (202) 672-5571
FAX: (202) 672-5399

**(16) "A duplicate of the application papers, certified as such," 37 C.F.R. § 1.740(a)(16).**

Enclosed is a certification that this application for patent extension, including its attachments, is being submitted as one original and one duplicate copy thereof (Exhibit D).

**(17) "An oath or Declaration as set forth in 37 C.F.R. § 1.740(b)," 37 C.F.R. § 1.740(a)(ii).**

The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached as Exhibit E.

Respectfully submitted,

26 May 1999
Date

H. C. Wegner Reg. No. 25,258
Harold C. Wegner
Reg. No. 25,258

# ATTACHMENT A

Copy of U.S. Patent 5,362,755

US005362755A

# United States Patent [19]

**Barberich et al.**

[11] **Patent Number: 5,362,755**

[45] **Date of Patent: Nov. 8, 1994**

[54] **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL**

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[21] Appl. No.: **163,581**

[22] Filed: **Dec. 7, 1993**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[5] ..... **A61K 31/135**
[52] **U.S. Cl.** ..... **514/649**; 514/826
[58] **Field of Search** ..... 514/649, 826

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

2255503 7/1992 United Kingdom .

OTHER PUBLICATIONS

R. T. Brittain et al., *Br. J. Pharmacol.*, 48:144–147 (1973).

C. J. Hawkins and G. T. Klease, *J. Med. Chemistry*, 16(7):856–857 (1973).

D. Hartley and D. Middlemiss, *J. Med. Chemistry*, 14(9):895 (1971).

C. K. Buckner and P. Abel, *J. Pharmacol. Exp. Ther.*, 189(3):616–625 (1974).

Tan et al., "Analysis of Salbutomol Enantiomers in Human Urine by Chiral High Performance Liquid Chromatography and Preliminary Studies Related to the Stereoselective Disposition Kinetics in Man", *J. Chromatogr.*, 422, 187–95 (1987).

Chemical Abstracts 89:123259m (1978).

*Primary Examiner*—Raymond J. Henley, III
*Attorney, Agent, or Firm*—Heslin & Rothenberg

[57] **ABSTRACT**

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

**7 Claims, No Drawings**

# METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jan. 5, 1990 now abandoned.

## DESCRIPTION

1. Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

## SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of $\alpha^1$[(-tert-butylamino) methyl]-4-hydroxy-m-xylene-$\alpha$, $\alpha'$-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

## Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(−) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

# ATTACHMENT B

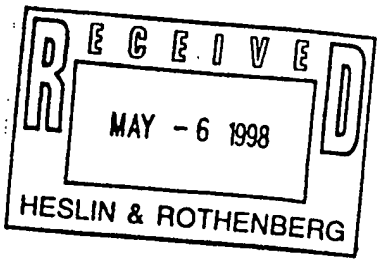
## Maintenance Documentation

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
002644

M75N4

HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203




701.027B

# MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

| ITM NBR | PATENT NUMBER | FEE CDE | FEE AMOUNT | SUR CHARGE | SERIAL NUMBER | PATENT DATE | FILE DATE | PAY YR | SML ENT | STAT |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 5,362,755 | 283 | 525 | ---- | 08/163,581 | 11/08/94 | 12/07/93 | 04 | YES | PAID |

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

| ITM NBR | ATTY DKT NUMBER |
|---|---|
| 1 | SPC8905 |

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:**
**COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

☆ U.S. GPO: 1998-437-690/79138

# ATTACHMENT C

## FDA Chronology of Significant Activities

**Chronology of Significant Activites Regarding IND 47,363 and NDA 20-837 for Xopenex™ (levalbuterol HCl) Inhalation Solution**

**(February 28, 1995, through March 25, 1999)**



| Date | Activity |
|---|---|
| February 28, 1995 | *IND* – Original IND Submission |
| March 28, 1995 | *IND* – Response to FDA Request of 3-27-95: Plasma sampling info in 28 d & 90 d oral & inhalation tox studies. |
| May 21, 1995 | *IND* – Protocol Amendment: New Investigator to Protocol 051.005.0 |
| October 9, 1995 | *IND* – FDA Minutes of 7-25-95 Meeting. Protocol Amendment: Change in Investigator for study 051-005 – Atlanta site |
| January 29, 1996 | *IND* – Information Amendment: Pharm/Tox (2 reports) |
| February 15, 1996 | *IND* – EOP2 Package, Revised Investigator's Brochure dated 2-17-95, Clinical Info, Draft Labeling, New Protocol 051-012, Request for End of Phase 2 Meeting |
| March 13, 1996 | *IND* – Response to FDA's requests for Draft Dog Inhalation Protocols |
| March 22, 1996 | *IND* – Response to FDA Request of 3-19-96 for Information: Amendment to Chemistry, Manufacturing & Controls Section of IND—new method of manufacture of drug substance; new manufacturer & updated documentation for (R)-Albuterol and (RS)-Albuterol .021% & .042%(w-w) |
| April 12, 1996 | *IND* – Revised draft of Protocol 051-012 in response to FDA's request of 4-10-96 |
| May 31, 1996 | *IND* –Sepracor Minutes for EOP2 Meeting held 4-25-96. |
| June 5, 1996 | *IND* - IND Annual Report (March 25, 1995 – March 27, 1996) |
| June 10, 1996 | *IND* – Protocol Amendment: New Protocol (051-006); CMC Amendment (S)-Albuterol |
| July 1, 1996 | *IND* – Protocol Amendment: New Protocol (051-024); Information Amendment: CMC for active comparator, (RS)-Albuterol Inhalation Solution; Contract Research Organization (PPD's) Responsibilities for 051-024 as item number 13 of Form 1571. |
| July 8, 1996 | *IND* – Protocol Amendment: Change in Protocol (051-024, Amendment No. 1) |
| July 9, 1996 | *IND* – Protocol Amendment: Change in Protocol (051-006, Amendment No. 1) |
| July 11, 1996 | *IND* – Information Amendment: CMC. Responses to (a) questions from 5-3-95 letter from FDA and (b) questions raised during EOP2 Meeting from Fax 7-1-96. |
| July 23, 1996 | *IND* – Protocol Amendment: Change in Protocol (051-006, Amendment No. 2) |
| July 29, 1996 | *IND* – Protocol Amendment: New Protocol (051-025); Response to the Division's Fax of July 1, 1996. |
| July 31, 1996 | *IND* – Protocol Amendment: New Protocol - Draft Pediatric Protocol (051-010) for FDA review |
| August 6, 1996 | *IND* – FDA Minutes of CDER Office of Pharmaceutical Science-Sepracor Inc. Pharmaceuticals Meeting on August 6, 1996. |
| August 12, 1996 | *IND* – IND Safety Report (051-006) – chest pain-pleurisy of viral etiology |
| August 12, 1996 | *IND* – IND Safety Report (051-024) – exacerbation of asthma |
| August 20, 1996 | *IND* – Protocol Amendment: New Investigators: Protocol 051-024 |
| August 27, 1996 | *IND* – Draft protocol 051-021 for FDA review |

**Chronology of Significant Activites Regarding IND 47,363 and NDA 20-837 for Xopenex™ (levalbuterol HCl) Inhalation Solution**

**(February 28, 1995, through March 25, 1999)**



| Date | Activity |
|---|---|
| September 12, 1996 | *IND* – IND Safety Report, Protocol 051-024, left face numbness, Dr. Tommy C. Sim, Texas |
| September 20, 1996 | *IND* – Protocol Amendment: New Investigators to Protocol 051-024 |
| October 18, 1996 | *IND* – Protocol Amendment: New Investigators to Protocol 051-024 |
| October 28, 1996 | *IND* – Information Amendment: CMC – lower dosage (0.156-0-312). Protocol Amendment: New Protocol (051-010). |
| November 4, 1996 | *IND* – Protocol Amendment: Change in Protocol (Amendment No. 2 to 051-024) |
| November 11, 1996 | *IND* – Protocol Amendment: Change in Protocol (Amendment No. 1 to 051-010) |
| November 18, 1996 | *IND* – Protocol Amendment: New Investigator J. Fink, Milwaukee) to protocol 051-024 |
| November 19, 1996 | *IND* – Protocol Amendment: Change in Protocol (Final amendment to protocol 051-021) |
| December 16, 1996 | *IND* – Protocol Amendment: New Investigators (R. Cohen, Lawrenceville, GA and S. Gawchik, Chester, PA) to protocol 051-024 |
| December 23, 1996 | *IND* – Protocol Amendment: Change in Protocol (Amendment No. 2 to Protocol 051-021) |
| December 24, 1996 | *IND* – Safety Report: Exacerbation of Asthma (ADR#961116.0051.1) |
| December 24, 1996 | *IND* – Safety Report: Exacerbation of Asthma (ADR#961114.0051.1) |
| January 8, 1997 | *IND* – Protocol Amendment: Change in Protocol (Amendment No. 3 to protocol 051-021) |
| January 9, 1997 | *IND* – Protocol Amendment: Additional new principal investigator (T Sim, Friendswood, TX) for 051-010 |
| January 15, 1997 | *IND* – Protocol Amendment: New Protocol (051-017) – Exercise Induced Protocol |
| January 27, 1997 | *IND* – Request for Pre-NDA meeting |
| January 28, 1997 | *IND* – Safety Report: Exacerbation of Asthma (ADR#970103.0051.1) |
| February 4, 1997 | *IND* – Request to consider Study 051-006 as an adequate cumulative dose safety study |
| February 20, 1997 | *IND* – USAN for (R)-albuterol HCl |
| February 20, 1997 | *IND* – Pre-NDA Meeting Package |
| March 12, 1997 | *IND* – Information Amendment: Pharm-tox |
| March 12, 1997 | *IND* – Pre-NDA Meeting Package Supplement |
| March 20, 1997 | *IND* – Response to FDA Request for information for Pre-NDA meeting |
| March 31, 1997 | *IND* – General Correspondence: Request for tradename review |
| April 15, 1997 | *IND* – Response to FDA Request for Information of 4-15-97: explanation for Levalbuterol NDA as a 505(b)(2) |
| April 16, 1997 | *IND* – Safety Report: Death (SAE # 970324.0051.1) |
| May 7, 1997 | *IND* – Protocol Amendment: Change in Protocol 051-017 (Amendments 1 & 2); Response to FDA's Request for Information in Fax dated 4-2-97 |

**Chronology of Significant Activites Regarding IND 47,363 and NDA 20-837 for Xopenex™ (levalbuterol HCl) Inhalation Solution**

**(February 28, 1995, through March 25, 1999)**



| Date | Activity |
|---|---|
| May 13, 1997 | *IND* – Protocol Amendment: Changes in Forms FDA 1572 for Protocol No. 051-024 |
| June 23, 1997 | *IND* – General Correspondence: Confirm levalbuterol NDA as a 505(b)(2) application |
| June 30, 1997 | *NDA* – Original NDA Submission |
| July 2, 1997 | *NDA* – Submission: Type 1 DMF (Original Submission), Sepracor Canada Ltd. |
| July 11, 1997 | *IND* – Protocol Amendment: Change in protocol (051-017 – Amendment No. 3 and revised Protocol #1) |
| July 17, 1997 | *NDA* – Submission: Summary of proposed product for planned submission of Multidose Vial formulation |
| July 21, 1997 | *IND* – General Correspondence: Re-submit Levalbuterol HCl Multidose Inhalation Solution Proposal and request for comments |
| July 22, 1997 | *IND* – Protocol Amendment: New Protocol No. 051-023 |
| July 24, 1997 | *IND* - IND Annual Report (March 28, 1996 – June 30, 1997) |
| August 13, 1997 | *IND* – Protocol Amendment: New Investigator (E. Israel, Boston) to 051-023 |
| September 2, 1997 | *IND* – Protocol Amendment: Change in Protocol (051-023 – Amendment No. 1) |
| September 4, 1997 | *NDA* – Submission: 90-Day Conference Request |
| September 15, 1997 | *NDA* – Submission: Clinical Site Inspection Packages for 051-024, Drs. Colton (FL), Edwards (NY), and Sim (TX) |
| September 17, 1997 | *NDA* – Submission: Copies of PAI cover letters sent to Dr. Ju |
| October 13, 1997 | *NDA* – Submission: Justification for the use of tradename, ZOPEN™ |
| October 21, 1997 | *NDA* – Submission: Responses to CMC comments dated August 13, 1997 |
| October 31, 1997 | *NDA* – Submission: Response to Request for Information: Clinical Documentation for Thomas Edwards, MD |
| November 4, 1997 | *NDA* – Submission: Final internal audit report for Thomas Edwards, MD |
| November 4, 1997 | *NDA* – Submission: Additional analysis of Study 051-024 requested by Dr. Nicklas on 10-31-97 |
| November 6, 1997 | *NDA* – Submission: Withdrawal of environmental assessment (V006, P001-032) and correspondence dated July 17, 1997 |
| November 20, 1997 | *NDA* – Submission: Section 9: 120-Day Safety Update |
| December 1, 1997 | *NDA* – Submission: Study 051-010 body weight considerations |
| December 8, 1997 | *NDA* – Submission: Request for tradename secondary evaluation |
| December 17, 1997 | *IND* – Information Amendment: CMC |
| December 22, 1997 | *IND* – Protocol Amendment: Change in Protocol (051-023 – Amendment No. 2) |
| December 23, 1997 | *IND* – Protocol Amendment: New Protocol – 051-027 (Proposed Phase 4 Study) |
| January 12, 1998 | *NDA* – Submission: Additional analysis of Study No. 051-024 Safety Data |
| January 21, 1998 | *NDA* – Submission: Proposed tradename for levalbuterol, XOPEN |
| January 23, 1998 | *NDA* – Submission: Request for tradename review-clarification |

**Chronology of Significant Activites Regarding IND 47,363 and NDA 20-837 for Xopenex™ (levalbuterol HCl) Inhalation Solution**

**(February 28, 1995, through March 25, 1999)**



| Date | Activity |
|---|---|
| February 20, 1998 | *NDA* – Submission: Clinical Site Inspection Package—Data for Howard Schwartz, MD (OH) |
| March 11, 1998 | *NDA* – Letter to FDA: Request for tradename secondary LNC evaluation XOPEN™ for Levalbuterol HCl |
| March 17, 1998 | *IND* – Protocol Amendment: Change in Protocol (Amendments to 051-027) |
| April 9, 1998 | *NDA* – Amendment: Submission of Additional Analysis of Study 051-024, safety data |
| April 10, 1998 | *IND* – Protocol Amendment: Change in Protocol (051-027) |
| May 13, 1998 | *NDA* – Clarifications/response to CPT's 483s concerning the Levalbuterol NDA stability data/proposal for follow-up |
| May 18, 1998 | *IND* – Protocol Amendment: New Investigators (051-027) |
| May 28, 1998 | *NDA* – Submission: CMC Amendment: Responses to May 4 and 20, 1998 IR letters and May 26, 1998, Stability Updates Amendment |
| June 16, 1998 | *NDA* – Letter to FDA: Amendment to NDA Patent Information, U.S. Patent No. 5,760,090 |
| June 18, 1998 | *IND* – Protocol Amendment: New Investigators (051-027) |
| June 26, 1998 | *NDA* – Submission: CMC Amendment – Remove Cipla as supplier of raw materials |
| July 1, 1998 | *NDA* – Letter from FDA: Approvable Letter and Patient Labeling |
| July 10, 1998 | *NDA* – Letter to FDA: Response to 7-1-98 Approvable Letter |
| July 20, 1998 | *NDA* – Submission: Updated Questions for 7-21-98 Teleconference |
| July 23, 1998 | *IND* – Protocol Amendment: New Investigators (051-027) |
| August 6, 1998 | *NDA* – Resubmission and Complete Response to Regulatory Action Letter of 1 July 1998 |
| September 18, 1998 | *IND* – Protocol Amendment: New Investigator (051-027) |
| September 24, 1998 | *NDA* – Submission: Response to FDA Communication of 31 August 1998 |
| September 25, 1998 | *IND* – Protocol Amendment: New Protocol (051-902 [CEP study]) |
| September 30, 1998 | *NDA* – Submission: Correction of albuterol aldehyde specification |
| October 19, 1998 | *NDA* – Submission: Request for teleconference to discuss recalculating PDUFA goal date of March 25, 1999 (as described in FDA letter of 10-7-98) to February 11, 1999 (as described in Sepracor fax of 10-16-98) and to discuss final labeling. |
| October 22, 1998 | *IND* – Protocol Amendment: New Investigators (051-902 [CEP study]) |
| November 10, 1998 | *IND* – Letter of Authorization to Incorporate by Reference, for IND 51,117/William Spiegel, MD |
| November 19, 1998 | *IND* – Protocol Amendment: New Investigators (051-902 [CEP study]) |
| December 2, 1998 | *IND* – Protocol Amendments: Change in Protocol (051-027), New Investigators |
| December 2, 1998 | *IND* – Annual Report (July 1, 1997 – June 30, 1998) |
| December 11, 1998 | *NDA* – Submission: Issuance of U.S. Patent No. 5,844,002 |

**Chronology of Significant Activites Regarding IND 47,363 and NDA 20-837 for Xopenex™ (levalbuterol HCl) Inhalation Solution**

**(February 28, 1995, through March 25, 1999)**



| Date | Activity |
|---|---|
| December 18, 1998 | *NDA* – Submission: Response to FDA request for diskettes containing CMC information from August 6, 1998; September 24 and 30, 1998 (2 diskettes and accompanying letter). |
| December 23, 1998 | *IND* – Protocol Amendment: New Investigators (051-902 [CEP Study]) |
| December 24, 1998 | *IND* – Protocol Amendment: New Investigators (051-027) |
| January 8, 1999 | *NDA* – Submission: Response to request (of 1-4-99) for electronic copy of CMC data in the 5-28-98 submission |
| January 28, 1999 | *NDA* – Submission: Information on Stability Testing—discontinuance of Consumer Product Testing Co. for stability testing of drug substance and drug product |
| January 29, 1999 | *NDA* – Submission: Electronic Copy of 1-28-99 Submission—Information on Stability Testing |
| February 16, 1999 | *IND* – Protocol Amendment: New Principal Investigator, 051-027 (Peter Economou, MD, Alberqueque) |
| February 24, 1999 | *NDA* – Submission: Acknowledgement of the fax of revised draft labeling received 2-23-99. Reference made to submissions of 8-6-98 and 9-24-98. |
| March 8, 1999 | *NDA* – Submission: Revised Draft Labeling, Version 03-08-99 |
| March 10, 1999 | *NDA* – Submission: Proposed Core Promotional Materials |
| March 15, 1999 | *IND* – Information Amendment: Pharmacology/ Toxicology (Document Nos. 051-820, 051-821, 051-486, 051-463, 051-476, and 051-465A) |
| March 18, 1999 | *NDA* – Submission: Response to FDA Communication Dated 15 March 1999 (CMC Comments)—includes updated stability data for the drug substance and drug product at the 24-month time interval |
| March 18, 1999 | *NDA* – Submission: Samples of cartons and foil pouch labels to replace those previously submitted on 24 September 1998, including foil pouch for the 0.63 mg/3mL vials, which changed since the September submission |
| March 22, 1999 | *NDA* – Submission: Safety Update and CMC Information (provides information requested during teleconferences of March 16 and March 19, 1999) |
| March 23, 1999 | *NDA* – Submission: Revised Draft Labeling, Version 03-23-99 (requested during teleconference of March 22, 1999) |
| March 24, 1999 | *NDA* – Submission: Commitment regarding package labeling (foil pouches) |
| March 25, 1999 | *IND* – Protocol Amendment: Protocol Concept–Submission of proposal to conduct pediatric study 051-031 |
| March 25, 1999 | *NDA* – FDA Approval Letter for NDA 20-837 |

# ATTACHMENT D

## Submission Certification

**BOX PATENT EXT.**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH, *et al.*

Assignee: Sepracor, Inc.

Issue Date: November 8, 1994

## CERTIFICATION

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

I, Harold C. Wegner, do hereby certify that this accompanying application for extension of the term of U.S. Patent 5,362,755 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and one duplicate copy thereof.

Respectfully submitted,

21 May 1999
Date

H. C. Wegner, Reg No. 29,768
for Harold C. Wegner
Reg. No. 25,258

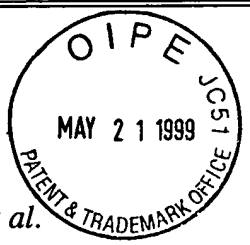
Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, D.C. 20007-5109
Tel: 202-672-5300
Fax: 202-672-5399

# ATTACHMENT E

## Declaration

**BOX PATENT EXT.**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE




Atty. Docket No. 046714/0113

In re: U.S. Patent No. 5,362,755

Patentee: Timothy J. BARBERICH, *et al.*

Assignee: Sepracor, Inc.

Issue Date: November 8, 1994

## DECLARATION

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

As agent for the owner of record of U.S. Patent 5,362,755 I declare that:

(1) I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have general authority from the owner of United States Patent 5,362,755 to act on behalf of the owner in patent matters;

(2) I have reviewed and understand the contents of the accompanying application, which is submitted pursuant to 37 C.F.R. § 1.740 for extension of U.S. Patent 5,362,755;

(3) I believe that U.S. Patent 5,362,755 is subject to extension pursuant to 37 C.F.R. § 1.710;

(4) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) I believe that U.S. Patent 5,362,755, for which this extension is sought, meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 5,362,755.

Respectfully submitted,

21 May 1999
Date

H. C. Post, Reg. No. 29,766
for Harold C. Wegner
Reg. No. 25,258

Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, D.C. 20007-5109
Tel: 202-672-5300
Fax: 202-672-5399


# ATTACHMENT F

Letters

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JUL 10 1996



Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Dear Mr. Wilson:

The attached application for patent term extension of U.S. Patent No. 4,309,445, which issued January 5, 1982, was filed on June 25, 1996, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, REDUX™ (dexfenfluramine hydrochloride), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156 if the approval of REDUX™ (dexfenfluramine hydrochloride) is considered to be the first permitted commercial use of the product. It is noted that the application argues that, although a racemate of REDUX™, fenfluramine (PONDIMIN®), has been previously approved, the prior approval of PONDIMIN® should not disqualify the approval of REDUX™ from being considered the first permitted commercial use of dexfenfluramine hydrochloride. See particularly Attachment E to the application for patent term extension.

Inquiries regarding this communication should be directed to Karin Tyson at (703) 306-3159.

Hiram A. Bernstein
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Project

cc: Charles E. Van Horn
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

kt

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service



Food and Drug Administration
Rockville MD 20857

NOV 21 1996

Re: REDUX™
Docket No. 96E-0265

Stephen G. Kunin
Deputy Assistant Commissioner for
Patent Policy and Projects
U.S. Patent and Trademark Office
Box Pat. Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231



Dear Mr. Kunin:

This is in regard to the application for patent term extension for U.S. Patent No. 4,309,445 filed by Interneuron Pharmaceuticals, Inc. under 35 U.S.C. § 156. The human drug product claimed by the patent is REDUX™ (dexfenfluramine hydrochloride), which was assigned New Drug Application (NDA) No. 20-344.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of this product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp. 1224 (E.D. Va. 1989), aff'd, 894 F.2d 392 (Fed. Cir. 1990).

The NDA was approved on April 29, 1996, which makes the submission of the patent term extension application on June 25, 1996, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A), we will then determine the applicable regulatory review period, publish the determination in the Federal Register, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely,

Ronald L. Wilson

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs

cc: Charles E. Van Horn
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315